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Birth Weight, Genetic Susceptibility, and Adulthood Risk of Type 2 Diabetes

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OBJECTIVE—Both stressful intrauterine milieu and genetic susceptibility have been linked to later-life diabetes risk. The current study aims to examine the interaction between low birth weight, a surrogate measure of stressful intrauterine milieu, and genetic susceptibility in relation to risk of type 2 diabetes in adulthood.

RESEARCH DESIGN AND METHODS—The analysis included two independent, nested case-control studies of 2,591 type 2 diabetic case subjects and 3,052 healthy control subjects. We developed two genotype scores: an obesity genotype score based on 32 BMI-predisposing variants and a diabetes genotype score based on 35 diabetes-predisposing variants.

RESULTS—Obesity genotype scores showed a stronger association with type 2 diabetes risk in individuals with low birth weight. In low-birth weight individuals, the multivariable-adjusted odds ratio (OR) was 2.55 (95% CI 1.34–4.84) by comparing extreme quartiles of the obesity genotype score, while the OR was 1.27 (1.04–1.55) among individuals with birth weight >2.5 kg (P for interaction = 0.017). We did not observe significant interaction between diabetes genotype scores and birth weight with regard to risk of type 2 diabetes. In a comparison of extreme quartiles of the diabetes gene score, the multivariable-adjusted OR was 3.80 (1.76–8.24) among individuals with low birth weight and 2.27 (1.82–2.83) among those with high birth weight (P for interaction = 0.16).

CONCLUSIONS—Our data suggest that low birth weight and genetic susceptibility to obesity may synergistically affect adulthood risk of type 2 diabetes.

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Accumulating evidence has shown that the risk of type 2 diabetes in later life might be programmed by intrauterine exposure to environmental stress such as malnutrition (1,2), which may cause physiological, epigenetic, or structural alterations related to poor development of pancreatic β -cell mass and function (3) or insulin resistance (4) in the offspring and subsequently increase the susceptibility to risk of type 2 diabetes during adulthood (1,2). Low birth weight, as a surrogate for prenatal malnutrition, is common in both developing and developed countries, with prevalence reaching 8% in the U.S. and 15.5%

worldwide (5). In epidemiology studies, low birth weight has consistently been related to increased diabetes risk (6–8).

Recent large-scale genome-wide association studies confirm that common variants in the human genome also contribute to the development of type 2 diabetes (9,10). Thus far, nearly 40 loci have been related to diabetes risk at the genome-wide significance level. In addition, genetic variants predisposing to obesity (11), the most important risk factor for type 2 diabetes, have also been found to be related to diabetes risk (12). These genetic variants may affect disease risk through influencing either β -cell function or insulin resistance.

Interestingly, only a few diabetes (13,14) or obesity (15) loci are directly related to birth weight and with quite complex effects: some type 2 diabetes risk alleles are associated with reduced (13) while some others with increased (14) birth weight. Those results suggest that the genetic variants and birth weight may affect the disease risk through different mechanisms. However, the pathways linking low birth weight or genetic variants to diabetes are interwoven. Therefore, we assume that these two types of risk factors may interact in determining risk of type 2 diabetes.

In this study, we assessed the potential interaction between birth weight and genetic susceptibility to type 2 diabetes and obesity on risk of type 2 diabetes in two independent prospective cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The genetic susceptibility was evaluated by combining all the identified common variants from recent genome-wide association studies.

RESEARCH DESIGN AND METHODS

The NHS was initiated in 1976, when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire. Since 1976, information on disease status and lifestyle factors had been collected from this cohort every 2 years. The HPFS was a prospective cohort study of 51,529 U.S. male health professionals aged 40–75 years at study initiation in 1986. Similarly, information about health and disease was assessed biennially with self-administered questionnaires. Blood was collected from 32,826 NHS members between 1989 and 1990 and from 18,159 HPFS members between 1993 and 1999 (16,17). Participants for the current study were selected from individuals who provided blood samples using a nested case-control study design (18,19). A total of 3,221 (1,467 case and 1,754 control) women and 2,422 men (1,124 case and 1,298 control) of European ancestry were included in the current analysis (18,19). All participants provided written informed consent, and the study was approved by the Human Research Committee at the Brigham and Women's Hospital and Harvard School of Public Health.

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Type 2 diabetes cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire (20,21). For cases before 1998, we used the National Diabetes Data Group criteria to define type 2 diabetes (22). We used the American Diabetes Association diagnostic criteria for type 2 diabetes diagnosis from 1998 onward (23). Control subjects were defined as those free of diabetes at the time of diagnosis for case subjects and remaining unaffected through follow-up (until 2006). We matched the case subjects to nondiabetic control subjects on age, month and year of blood draw, and fasting status in NHS and HPFS, respectively. The validity of self-reported type 2 diabetes diagnosis has previously been documented in the NHS. In a random sample of 62 cases that were confirmed by the supplementary questionnaire, 61 cases (98%) were reconfirmed after the subjects' medical records were reviewed by an endocrinologist blinded to the supplementary questionnaire (21). We conducted a similar validation study in the HPFS: of 59 type 2 diabetes case subjects who reported newly diagnosed diabetes between 1996 and 1998, 57 (97%) were reconfirmed by medical records (20). Moreover, we conducted another substudy to assess the specificity of self-reported diabetes status. In a random sample of participants ($n = 200$) who reported no diabetes, only one participant (0.5%) had an elevated fasting plasma glucose or plasma fructosamine concentration in the diabetic range, and her concentrations were barely above the diagnostic cutoffs (20,24).

Assessment of birth weight

Participants in NHS (16) and HPFS (17) cohorts were requested to provide their birth weight on the 1992 and the 1994 questionnaires, respectively. The actual birth weights of 220 randomly selected participants were obtained from state birth records for validation (25). The Spearman correlation between self-reported and recorded birth weight was 0.74 ($P < 0.001$). In addition, 70% of the participants reported the same birth weight category as was obtained from state birth records. We classified the participants with birth weight ≤ 2.5 kg (5.5 lb) as having low birth weight (25).

Among the 5,643 participants, 1,689 did not report their birth weight and were excluded from the analysis regarding low birth weight. The proportion of people

with birth weight data was comparable between the diabetic and the control groups (69.8 vs. 70.3%, respectively; $P = 0.7$). Participants who did not recall their birth weight were more elderly. No other characteristics were different between the participants with and without their birth weight information.

Assessment of covariates

Information about anthropometric data, smoking status, alcohol intake, menopausal status, postmenopausal hormone therapy (women only), and family history of diabetes was derived from the baseline questionnaires (16). We calculated BMI as weight in kilograms divided by the square of height in meters. Physical activity was expressed as METs per week using reported time spent on various activities—weighting each activity by its intensity level—in 1986 questionnaires for men and women. The validity of the self-reported body weight and physical activity data has previously been described (26–28).

Genotyping and imputation

DNA was extracted from the buffy coat fraction of centrifuged blood using a commercially available kit (QIAmp Blood kit; Qiagen, Chatsworth, CA). We selected 32 established BMI-predisposing single nucleotide polymorphisms (SNPs) (Supplementary Table 1) and 35 established diabetes-predisposing SNPs (Supplementary Table 2). SNP genotyping and imputation have previously been described in detail (18,19). Briefly, samples were genotyped and analyzed using the Affymetrix Genome-Wide Human 6.0 array (Affymetrix; Santa Clara, CA) and the Birdseed calling algorithm. We used MACH (<http://www.sph.umich.edu/csg/abecasis/MACH>) to impute SNPs on chromosomes 1–22 with NCBI build 36 of Phase II HapMap CEU data (release 22) as the reference panel.

Genotype score computation

The obesity and diabetes genotype scores were calculated, respectively, on the basis of the 32 and 35 SNPs by using a previously described weighted method (19). We assumed that each SNP in the panel acts independently in an additive manner. Each SNP was weighted by β -coefficients obtained from published meta-analyses (9,11). (The original β value can be found in the references listed in Supplementary Tables 1 and 2.) The genotype score was calculated by multiplying each

β -coefficient by the number of corresponding risk alleles (best estimated number of alleles for imputed SNPs) and summing up the products. Because this produced a score out of 8.78 for obesity genotype score and 7.49 for diabetes genotype score (twice the sum of the β -coefficients), all values were divided by 8.78 (or 7.49) and multiplied by 32 (or 35) to make the genetic score easier to interpret. Most of the SNPs included in the genetic score were genotyped or had a high imputation quality score (MACH $r^2 \geq 0.8$) (Supplementary Tables 1 and 2).

Statistical analyses

χ^2 tests and t tests were used for comparison of proportions and means between case and control subjects for baseline characteristics. We used logistic regression to estimate the odds ratio (OR) for risk of type 2 diabetes, adjusting for age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥ 15.0 g/day), menopausal status (pre- or postmenopausal [never, past, or current menopausal hormone use] [women only]), and physical activity (quintiles). Because the results were similar between men and women, similar analyses were repeated after pooling individual-level data from the two cohorts and further adjusting for sex. To examine the accumulative effects of the genotype scores, we compared the type 2 diabetes risk across the quartiles of the genotype scores according to their distribution in the study samples. To test for linear trends across quartiles of genotype score, we modeled the quartile medians as a continuous variable. We also performed the linear relation analysis between the genotype scores (as continuous variables) and risk of type 2 diabetes by using a restricted cubic spline regression model (29). We tested the interaction by comparing the log likelihood of the model including interaction term with the model that contained only the main effects.

To test the joint effect of the obesity genotype score and diabetes genotype score, we divided the sample into high and low genotype score based on the median value in control subjects and then classified participants into four subgroups according to the joint classification of obesity genotype score and diabetes genotype score: both low, only with high obesity genotype score, only with high diabetes genotype score, and both high. We then examined the association between the joint genotype score and type 2 diabetes stratified by birth weight.

We did a sensitivity analysis after excluding the individuals with birth weight >4.5 kg. Another sensitivity analysis only included the SNPs that were genotyped or had a high imputation quality score (MACH $r^2 \geq 0.8$). We considered two-sided P values <0.05 to be statistically significant. Adjustments for multiple comparison tests were not performed because SNPs were selected on the basis of a priori hypothesis. Statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC).

RESULTS—Baseline characteristics of case and control subjects in the NHS (women) and HPFS (men) are shown in Table 1. In both men and women, type 2 diabetic patients had significantly higher BMI, engaged in less physical activity, were more likely to smoke, and more likely had a family history of diabetes compared with control subjects. Women with type 2 diabetes consumed less alcohol and were more likely to be postmenopausal than their counterparts in the control group.

The OR for type 2 diabetes associated with a one-point increase of the obesity genotype score, corresponding to one BMI-increasing allele and was 1.03 (95% CI 1.01–1.05) in men, 1.03 (1.02–1.05) in women after adjustment for age (Table 2). The age-adjusted OR of type 2 diabetes associated with each additional diabetes genotype score was 1.10 (1.08–1.12) in men and 1.06 (1.04–1.08) in women. The linear relation analysis indicated that the genotype scores were linearly related to elevated type 2 diabetes risk (P for linearity = 0.001 for obesity genotype score and <0.0001 for diabetes genotype score). Further adjustment for physical activity, smoking, alcohol drinking, menopausal status (women only), and family history of diabetes did not materially change the associations of the obesity and diabetes genotype scores and type 2 diabetes risk. Further adjustment for BMI abolished the association between the obesity genotype score and type 2 diabetes but did not significantly change the association for diabetes genotype score.

We then analyzed the interaction between birth weight and the genetic risk scores for obesity or diabetes in relation to risk of type 2 diabetes. Because the results were highly consistent in men and women, data from the two cohorts were pooled together (Table 3). We observed significant interaction between birth weight (low versus high; defined by 2.5 kg) and the obesity genotype score

Table 1—Characteristics of type 2 diabetes case and control subjects at baseline

	Men			Women		
	Case subjects	Control subjects	P	Case subjects	Control subjects	P
<i>n</i>	1,124	1,298		1,467	1,754	
Age (years)	55.1 ± 8.6	55.0 ± 8.4	0.65	43.5 ± 6.7	43.1 ± 6.8	0.08
BMI (kg/m ²)	27.7 ± 4.0	25.0 ± 2.7	<0.001	27.4 ± 5.0	23.5 ± 3.9	<0.001
Family history of diabetes	36.8	15.9	<0.001	49.6	22.1	<0.001
Current smokers	11.8	7.3	<0.001	29.5	20.8	<0.001
Alcohol intake (g/day)	11.2 ± 16.2	12.1 ± 15.3	0.18	4.4 ± 9.1	6.6 ± 10.0	<0.001
Physical activity (MET h/week)	14.6 ± 19.0	21.1 ± 25.2	<0.001	11.7 ± 15.3	14.3 ± 18.7	<0.001
Postmenopausal				35.0	31.3	0.01
Postmenopausal hormone use				28.8	28.9	0.97
Low birth weight (≤2.5 kg)	6.8	5.7	0.39	12.1	9.7	0.06

Data are age-adjusted means ± SD or % unless otherwise indicated.

with regard to risk of diabetes, adjusting for age and other covariates (P for interaction = 0.017). In participants with low birth weight, the OR was 2.55 (95% CI 1.34–4.84) comparing the highest quartile of obesity genotype score with the lowest quartile. In participants with high birth weight, the OR was 1.27 (1.04–1.55) comparing these two extreme quartiles. Further adjustment for BMI attenuated the associations among low-birth weight individuals (OR 1.93 [0.95–3.83] comparing the two extreme quartiles, P for trend = 0.04) and abolished the association among individuals with high birth weight (1.0 [0.8–1.23], P for trend = 0.8; P for interaction = 0.06).

We did not observe significant interaction between diabetes genotype score and birth weight with regard to type 2 diabetes risk (Table 3). Comparing individuals of the top with those of the bottom quartile of the diabetes genotype score yielded the following: the multivariable-adjusted OR was 3.80 (95% CI 1.76–8.24) among low-birth weight individuals and 2.27 (1.82–2.83) among individuals with birth weight >2.5 kg. However, test for interaction was marginal (P for interaction = 0.16). Further adjustment of the family history of diabetes did not change the results materially. We then examined the joint effects of low birth weight and the genotype scores on type 2 diabetes risk (Supplementary Fig. 1). Individuals with both low birth weight and the top quartile of genotype score had the highest odds of type 2 diabetes.

We also performed birth weight-stratified analysis for the combined genotype score of obesity and diabetes (Table 4). Among individuals with low birth weight, the multivariate-adjusted OR of type 2 diabetes was 3.32 (95% CI 1.17–6.61) for those only with high obesity genotype score, 3.16 (1.58–6.33) for those only with high diabetes genotype score, and 4.7 (2.34–9.45) for those with both high scores compared with those with both low scores. Among the individuals with high birth weight, the corresponding ORs were 1.15 (0.94–1.42), 1.42 (1.17–1.74), and 1.72 (1.41–2.1), respectively (P for interaction = 0.05).

We did sensitivity analyses by excluding individuals whose birth weight was >4.5 kg or by excluding SNPs with a low imputation quality score (MACH $r^2 < 0.8$). The results were not materially changed.

CONCLUSIONS—In two nested case-control studies from prospective cohorts of men and women, we observed consistent associations of obesity genotype score and diabetes genotype score with risk of type 2 diabetes. We observed significant interaction between birth weight and obesity genotype score in predicting diabetes, and the genetic effects were more pronounced in low-birth weight individuals than in those with high birth weight.

The association between genetic susceptibility and risk of type 2 diabetes presented in our study was in line with the

Table 2—Association between genotype scores and risk for type 2 diabetes in men and women

		Quartile of score				P
	Continuous score	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)	for trend
Obesity genotype score						
Men						
n		561	596	612	653	
Median (range)		24.7 (16.6–26.4)	27.8 (26.5–29.0)	30.3 (29.1–31.6)	33.5 (31.7–41.9)	
Age adjusted	1.03 (1.01–1.05)	1.00	1.16 (0.92–1.47)	1.13 (0.90–1.42)	1.38 (1.10–1.73)	0.01
Multivariate adjusted*	1.03 (1.01–1.06)	1.00	1.21 (0.95–1.54)	1.16 (0.91–1.48)	1.44 (1.14–1.83)	0.006
Women						
n		733	793	849	846	
Median (range)		24.6 (14.8–26.4)	27.8 (26.5–29.0)	30.3 (29.1–31.9)	33.9 (32.0–43.3)	
Age adjusted	1.03 (1.02–1.05)	1.00	1.23 (1.00–1.51)	1.36 (1.11–1.65)	1.41 (1.16–1.72)	0.0004
Multivariate adjusted*	1.04 (1.02–1.06)	1.00	1.15 (0.93–1.43)	1.28 (1.04–1.59)	1.41 (1.14–1.75)	0.0009
Diabetes genotype score						
Men						
n		491	551	634	746	
Median (range)		32.6 (22.6–34.3)	35.8 (34.31–37.0)	38.3 (37.1–39.6)	41.8 (39.7–52.0)	
Age adjusted	1.10 (1.08–1.12)	1.00	1.37 (1.07–1.77)	1.88 (1.47–2.39)	2.54 (2.00–3.21)	<0.0001
Multivariate adjusted*	1.11 (1.08–1.13)	1.00	1.43 (1.07–1.91)	1.88 (1.42–2.49)	2.76 (2.10–3.62)	<0.0001
Women						
n		682	799	841	899	
Median (range)		32.5 (23.9–34.3)	35.9 (34.32–37.0)	38.5 (37.1–39.9)	41.8 (39.9–51.2)	
Age adjusted	1.06 (1.04–1.08)	1.00	1.50 (1.22–1.85)	1.66 (1.35–2.04)	1.91 (1.56–2.34)	<0.0001
Multivariate adjusted*	1.08 (1.05–1.10)	1.00	1.47 (1.15–1.88)	1.76 (1.38–2.25)	2.13 (1.67–2.70)	<0.0001

Data are OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, family history of diabetes (yes or no), smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥ 15.0 g/day), physical activity (quintiles), menopausal status (women only), and BMI (for diabetes gene scores only).

findings of other studies (12,19). A genetic score based on 12 obesity-predisposing common genetic variants was associated with risk of incidence of type 2 diabetes (12). In the current study, we updated the obesity genotype score to included 32 SNPs and found similar results. Our previous study reported the joint effect of 10 diabetes-associated common genetic variants on the development of type 2 diabetes (19). In the current study, the

computation of the diabetes genotype scores was expanded by inclusion of 25 newly identified loci. The updated genotype scores represent broader characteristics of genetic risk profile and account for more variation in disease risk. Each additional BMI-increasing allele in the obesity genotype score was associated with a 3–4% (95% CI 1–6%) increased odds of developing type 2 diabetes, while each additional diabetes genotype score,

corresponding to one risk allele, was associated with an 8–11% (4–13%) increased odds of developing type 2 diabetes.

Intriguingly, we observed that the overall genetic susceptibility to obesity showed stronger associations with diabetes risk among participants with low birth weight than among those with high birth weight. Two previous studies investigated the interaction between birth weight and genetic factors with regard to BMI. One

Table 3—Association between BMI and diabetes genotype scores and risk for type 2 diabetes according to birth weight in pooled analysis of men and women

	<i>n</i>	Quartile of score				<i>P</i>
Birth weight (kg)	(case/control subjects)	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)	for trend
Obesity genotype score*						
≤2.5	174/169	1.00	1.23 (0.63–2.40)	2.06 (1.07–3.97)	2.55 (1.34–4.84)	0.002
>2.5	1,540/1,878	1.00	1.12 (0.91–1.37)	1.22 (1.00–1.48)	1.27 (1.04–1.55)	0.01
<i>P</i> for interaction						0.017
Diabetes genotype score*						
≤2.5	174/169	1.00	2.01 (0.93–4.32)	3.26 (1.47–7.22)	3.80 (1.76–8.24)	0.0006
>2.5	1,540/1,878	1.00	1.40 (1.11–1.76)	1.51 (1.20–1.89)	2.27 (1.82–2.83)	<0.0001
<i>P</i> for interaction						0.16

Data are multivariate-adjusted OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥ 15.0 g/day), physical activity (quintiles), menopausal status (women only), and BMI (for diabetes gene scores only).

Table 4—Association between joint genotype scores and risk for type 2 diabetes according to birth weight in pooled analysis of men and women

Joint genotype score					P for trend
BMI genotype score	Low	High	Low	High	
Diabetes genotype score	Low	Low	High	High	
Birth weight (kg)*					
≤2.5	1.00	3.32 (1.17–6.61)	3.16 (1.58–6.33)	4.70 (2.34–9.45)	<0.0001
>2.5	1.00	1.15 (0.94–1.42)	1.42 (1.17–1.74)	1.72 (1.41–2.1)	<0.0001
P for interaction					0.05

Data are OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), menopausal status (women only), and physical activity (quintiles).

found that the effect of risk alleles of SNPs in the *FTO* gene was more evident among individuals with low birth weight than among those with high birth weight (30). The other study did not find a significant interaction between birth weight (low, medium, or high) and obesity genotype score (based on 24 SNPs) in prediction of adult BMI in Danish subjects (*P* for interaction = 0.07) (31). The birth weight–gene interaction in relation to type 2 diabetes was tested in one study based on nine diabetes risk alleles, which showed that the individuals with the lowest birth weight and the most high-risk genotypes had the greatest risk of type 2 diabetes (32). These observations, including ours, suggest that low birth weight may strengthen the deleterious effects of genetic variants on the development of obesity or type 2 diabetes in later life. As shown in the present study, high obesity genetic susceptibility and high diabetes genetic susceptibility were jointly associated with a 72% increase in the odds of developing type 2 diabetes in individuals with high birth weight, while among low-birth weight individuals, the increase in the odds of developing type 2 diabetes was 370%.

The potential mechanisms underlying the birth weight–gene interactions remain unclear. The fetal programming hypothesis postulates that early life events play a powerful role in influencing later susceptibility to chronic diseases including type 2 diabetes (1,2). Low birth weight reflects intrauterine growth restriction, which may induce poor development of pancreatic β -cell mass and function (3), retarded skeletal muscle development (33), changed set point of the hypothalamic-pituitary-adrenal axis (34), or epigenetic alterations such as DNA

methylation (35). These alterations may subsequently affect insulin secretion or insulin resistance. Of note, all these changes may overlap with pathways linking the genetic variations to the development of type 2 diabetes (2), making the interactions between low birth weight and genetic factors possible. Our data indicate that the obesity-associated genetic variants, which are more closely related to insulin resistance (9), are more likely modulated by birth weight status than the type 2 diabetes-associated genetic variants, which are more tightly related to insulin secretion (β -cell function).

A major strength of the current study is our consistent findings from two well-established large prospective cohorts. The minimal population stratification in our study samples reduces the potential bias due to heterogeneous genetic structure (18). Several limitations deserve comments. First, the genetic variants only account for a small fraction of interindividual variation in BMI and diabetes risk. Second, birth weight was not available for one-third of participants in NHS and HPFS. This may reduce our power to detect the moderate interaction. Since characteristics of the individuals with missing birth weight were comparable to those who reported birth weight, the missing data are unlikely to artifactually affect the associations (36).

In conclusion, our data suggest that low birth weight and genetic susceptibility to obesity may synergistically affect risk of type 2 diabetes in adulthood. Our findings highlight the importance of more extensive intervention in the low-birth weight population, especially in those with a high-risk genetic profile, to reduce diabetes risk in later life. Future studies

are warranted to investigate the potential mechanisms and verify our findings, especially in other ethnicities.

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Y.L. and Q.Q. designed the study, contributed to the data analysis and interpretation of data, reviewed the manuscript, and wrote the first draft of the manuscript. T.W. contributed to the data analysis and reviewed the manuscript. F.B.H. and L.Q. designed the study, contributed to the data collection and analysis and interpretation of data, reviewed the manuscript, and supervised the study. L.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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